2004; 127:950–956). The sensitivity for low-grade dysplasia in the fecal DNA assay used in this study was at best 67%. Furthermore, owing to limited power in the subgroup analyses, the lack of an effect upon marker levels by disease duration, severity and extent of disease, and presence of concomitant PSC could be falsely negative.

Overall, fecal DNA testing seems to be a promising alternative to colonoscopy for screening and surveillance purposes. Stool assay may be useful for early detection of IBD-CRN, and could also help to guide the frequency of colonoscopy surveillance to tailor individual risk. Larger studies are needed, however, to confirm the results demonstrated in this study, as well as to provide the power for greater sensitivity in subgroup analyses.

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REGRESSION OF CIRRHOSIS WITH LONG–TERM TENOFOVIR TREATMENT

Marcellin P, Gane E, Buti M, et al. **Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468–475.**

Cirrhosis is the common final path of different chronic liver diseases. A couple of decades ago, cirrhosis was considered an irreversible state. Since the development of antiviral therapy for chronic hepatitis B and C, it has been observed that liver fibrosis, and to certain extent cirrhosis, can regress if the underlying etiology is under control. However, high-quality data to document this phenomenon are scarce.

In a recent paper, Marcellin et al reported the results of long-term tenofovir disoproxil fumarate treatment in patients with chronic hepatitis B (Lancet 2013;381:468–475). Tenofovir is among the most potent antiviral agents against hepatitis B virus (HBV). In the original registration trial involving 266 patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B and 375 patients with HBeAg-negative chronic hepatitis B, tenofovir demonstrated superior antiviral efficacy to adefovir dipivoxil (N Engl J Med 2008;359:2442–2455). Among HBeAg-positive patients, 76% of those treated with tenofovir and 13% of those treated with adefovir had HBV DNA suppressed below 69 IU/mL at week 48 ($P < .001$). Corresponding figures in HBeAg-negative patients were 93% and 63%, respectively ($P < .001$).

After week 48, patients in both groups continued tenofovir regardless of initial treatment assignment and were prospectively followed for 8 years. The current report by Marcellin et al was a planned analysis at 5 years (Lancet 2013;381:468–475). Although follow-up liver biopsy was optional, this study was remarkable in that 489 of the original 641 randomized patients completed 5 years of follow-up, and 348 patients (54% of the original cohort) also agreed to repeat liver biopsy at 5 years. Therefore, this study provided valuable data on the histologic benefits of long-term antiviral therapy.

The majority of patients had marked reduction in hepatic necroinflammation. The proportion with no or mild necroinflammation (Knodell score $\leq$ 3) increased from 8% at baseline to 80% at 5 years. Similarly, fibrosis also improved with time. No or mild fibrosis was found in 39% at baseline and 63% at 5 years. The proportion with pronounced bridging fibrosis or cirrhosis (Ishak stage 4–6) decreased from 38% to 12%. Altogether, 51% had improvement in fibrosis stage. Among 96 patients with cirrhosis at baseline, 71 (74%) had regression of cirrhosis, 70 of whom also showed improvement in Ishak fibrosis score by $\geq$2 points. Low body mass index (<25 kg/m^2) was the only independent factor associated with regression of cirrhosis.

In addition, 73% of HBeAg-positive and 85% of HBeAg-negative patients had normal alanine aminotransferase at 5 years. By intention-to-treat analysis, 65% of HBeAg-positive and 83% of HBeAg-negative patients had HBV DNA suppressed to $<$69 IU/mL. Of HBeAg-positive patients, 40% achieved HBeAg seroconversion. No drug-resistant mutant was detected.

Because of structural similarities between tenofovir and adefovir, nephrotoxicity and bone loss have been a concern. However, in this 5-year study, only 1 of 585 patients had creatinine clearance of $<$50 mL/min, and 7 (1%) patients had serum phosphorus of $<$0.65 mmol/L.

Comment. Regression of fibrosis has been observed ever since effective antiviral therapy became available. In a small study of 20 chronic hepatitis B patients treated with lamivudine for 1 year, 7 had improvement in fibrosis, 12 had static disease, and only 1 had progression from Knodell stage 0 to stage 1 disease (J Hepatol 1999;30:743–748). Subsequent studies largely supported the initial observation. In another study of 69 patients treated with entecavir, liver biopsy was repeated after a median of 6 years (range, 3–7; Hepatology 2010;52:886–893). Overall, 88% had improvement in fibrosis, and 58% had a reduction in Ishak fibrosis score by $\geq$2 points. All 10 patients with advanced fibrosis or cirrhosis at baseline had improvement in fibrosis stage. The current study by Marcellin et al adds further proof by including a large number of patients with repeated liver biopsies. In particular, the study included a sizable cohort of cirrhotic patients.

Is this unequivocal evidence of cirrhosis regression? Although there is little doubt that fibrosis can improve with treatment, the reversibility of cirrhosis remains controversial. Cirrhosis involves not only deposition of fibrous tissue, but also changes in liver architecture. In addition, studies with serial liver biopsies are not foolproof. Because a typical liver biopsy specimen only represents 1/50,000 of the entire liver volume, sampling variability is common. If the less severe area is biopsied at the second

assessment, a patient may erroneously be labeled to have regression of cirrhosis despite no change in disease status.

Current data, however, suggest that regression of cirrhosis is genuine at least in some cases. In a study of 195 chronic hepatitis B patients who underwent per-protocol paired liver biopsies in clinical trials, 100 had histologic response defined as a $\geq$2-point improvement in Knodell histologic activity index without worsening of fibrosis (Clin Gastroenterol Hepatol 2009;7:1113–1120). Hepatocellular carcinoma or cirrhotic complications only occurred in 1% of the patients with histologic response, compared with 12% of those without after a median follow-up of 7 years. No patient with regression of cirrhosis developed complications, compared with 30% of those who continued to have cirrhosis at the second biopsy. In addition, lamivudine monotherapy in patients with advanced fibrosis or cirrhosis is superior to placebo in preventing hepatocellular carcinoma and worsening of Child-Pugh score (N Engl J Med 2004;351:1521–1531). Among patients with decompensated liver cirrhosis, antiviral therapy may also result in delisting from transplantation list because of clinical improvement, and seems to improve the overall survival (Gastroenterology 2002;123:719–727; Hepatology 2011;54:91–100; J Viral Hepat 2012;19:732–743). Antiviral therapy also reduces portal pressure in some cirrhotic patients (J Hepatol 2009;51:468–474). Although none of these studies provide unequivocal evidence of cirrhosis regression, the clinical benefit of antiviral therapy is consistently observed.

If we agree that antiviral therapy can improve the histology and clinical outcome of cirrhotic patients, what is next? A number of observational studies suggest that cirrhotic patients with incomplete HBV DNA suppression are still at increased risk of hepatocellular carcinoma and cirrhotic complications (Gut 2013;62:760–765; Hepatology 2013 Feb 6 doi:10.1002/hep.26301 [Epub ahead of print]). Unfortunately, a proportion of patients will still have incomplete HBV DNA suppression despite potent antiviral drugs like entecavir and tenofovir (Aliment Pharmacol Ther 2012;35:1326–1335; Lancet 2013;381:468–475). The optimal treatment strategy in this setting, including the possibility of combination therapy (Gastroenterology 2012;143:619–628), remains to be defined.

It is also interesting to note that patients who failed to achieve regression of cirrhosis in the study by Marcellin et al were more likely to be overweight or obese. In recent years, nonalcoholic fatty liver disease has emerged as the most common cause of abnormal liver biochemistry worldwide (Gastroenterology 2011;140:124–131; Gut 2012;61:409–415) and the third leading indication for liver transplantation in United States (Gastroenterology 2011;141:1249–1253). It is important to remember that HBV may not be the sole driver of disease activity in some patients.

Finally, although we are satisfied with the safety and efficacy of entecavir and tenofovir, we should not forget the financial and psychological burden of long-term antiviral therapy on our patients. In the years ahead, efforts should be made to develop effective yet finite treatment for chronic hepatitis B. In addition, antiviral therapy lowers but does not eliminate the risk of hepatocellular carcinoma. Further knowledge in fibrosis and hepatocarcinogenesis will allow us to develop effective secondary prevention against hepatocellular carcinoma and cirrhotic complications.

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